REMARKS

Claims 29-37, 39 and 41-46 are pending in this application. Claims 1-28, 38 and 40 have been canceled without prejudice to or disclaimer of the subject matter contained therein.

Independent claim 29 is directed to a method for determining one or more kinetic parameters of binding between a first binding member and a second binding member comprising: simultaneously adsorbing the first binding member to a surface at a plurality of microspots, the adsorbing comprising activating the surface of at least one microspot by presenting thereto a chemical activating substance, the activating comprising forming a first channel around a region containing the at least one microspot, introducing a solution containing the activating substance into the channel, and removing excess activating solution from the channel, adsorbing the first binding member to the at least one microspot, and deactivating the at least one microspot; simultaneously presenting the second binding member at a plurality of concentrations to the first binding member at the plurality of microspots, there being a plurality of combinations of first binding member surface density and second binding member concentrations among the plurality of microspots; simultaneously obtaining one or more kinetic parameters indicative of a binding reaction between the first and second binding members at each of the plurality of microspots to produce a kinetic analysis of the binding, the binding being detected by a biosensor detection method; simultaneously obtaining reference data from a plurality of interspots, each of the interspots located at a surface between at least two or more the microspots; and processing the binding kinetic parameters and the reference data to obtain one or more kinetic parameters characteristic of the binding

between the first and second binding members, wherein the plurality of bindings carried out does not require a regeneration step. Claims 30-36 and 43-45 depend, either directly or indirectly, from claim 29.

Claim 37 is directed to a method for localizing a molecular species at each of two or more microspots on a surface, comprising: activating a microspot surface by: forming a first channel around the region containing the microspot; introducing a solution containing an activating substance into the channel; and removing excess activating solution from the channel; simultaneously adsorbing a molecular species to each of the two or more microspots, the adsorbing comprising forming at least two further channels, each being perpendicular to the first channel; simultaneously introducing a solution containing the molecular species into the channel; and optionally deactivating the microspot, wherein the molecular species localized on the two or more microspots may be the same in each of the microspots or different in each of the microspots, and wherein the molecular species may be adsorbed at identical or different surface densities to each of the microspots. Claims 39, 41, 42 and 46 depend, either directly or indirectly, from claim 37.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. Interview

Applicants kindly thank Examiner Lam for the telephone interviews conducted between the Examiner and Applicants' undersigned representative. During the interviews, both the presently claimed subject matter and the outstanding rejections were discussed. Of note, Applicants representative and the Examiner discussed the meaning of the term simultaneously according to the claimed subject matter. Contrary to the Examiner's assertion in the interview summary mailed on July 7, 2010, no agreement was reached with regard to the term simultaneously. For a detailed discussion of the term simultaneously, please *see* sections II and III below.

II. At page 2 of the Official Action, claims 29 and 37 have been objected to.

The Examiner objects to claims 29 and 37 because allegedly "there needs to be more than one member for there to be simultaneous adsorbing." *See* the Official Action at page 2, claim objections.

Applicants respectfully submit that the Examiner's interpretation of the claimed subject matter is flawed. In this regard, Applicants submit that the term "simultaneously" in the portions of claim 29 and 37 that the Examiner refers to in the objection does not necessarily refer to adsorbing more than one first binding member. In contrast, the term "simultaneously" may refer to, for example, adsorbing the first binding member at the plurality of microspots, all at the same time, i.e., simultaneously. Therefore, Applicant submits that the term "member" does not need to be replaced by the term "members".

Support for Applicants interpretation can be found in the as-filed specification, for example, at page 4, lines 18-28, which provides that:

> a single probe species is adsorbed to microspots on a surface such as an SPR surface under a plurality of conditions, for example at different concentrations or pH, in order to obtain different probe densities. Some conditions may be repeated in order to obtain density duplicates. A single target species is then presented to the microspots at a plurality of concentrations. A plurality of probe density and target concentration combinations is thus obtained. The pluralities of reactions are monitored simultaneously and signals indicative of the binding reactions are obtained and analyzed so as to produce a kinetic analysis of the binding. The kinetic analysis may comprise of, for example, calculating an association constant or a dissociation constant or affinity constant for the binding of the probe to the target.

In other words, Applicants submit that a single binding member, i.e., a single probe species, may be adsorbed to several microspots at the same time. This means that, contrary to the Examiner's assertion, the term member in claims 29 and 37 does not need to be replaced with the term "members."

In view of the foregoing, Applicants submit that the claims are fully supported by the specification. Accordingly, reconsideration and withdrawal of this rejection is requested.

III. At page 3 of the Official Action, claims 29-31, 33, 35-37, 41-43 and 46 are rejected under 35 USC § 103(a) as being unpatentable over Winkler et al. (US Patent No. 5,384,261), in view of Ivarsson (US Patent No. 6,493,097) and further in view of Lambert (US Patent Application Publication No. 20060210984).

The Examiner asserts that it would have been obvious to modify the subject matter described Winkler et al. to provide calibration spots in a line between lines of analyte reaction spots because it provides for the advantage of normalizing or calibrating for variations in a signal intensity of binding reactions as taught by Lambert.

In view of the following, these rejections are respectfully traversed.

To establish a *prima facie* case of obviousness, the Examiner must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc.,* 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, 550 U.S. 398 at 417.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Applicants respectfully submit that a *prima facie* case of obviousness has not been established because Lambert is not prior art against the presently pending claims within the meaning of 35 USC § 103(a). Further, assuming *arguendo* that Lambert et al. is proper prior art against the present claims, a *prima facie* case of obviousness has not

been established because, whether taken alone or together, the cited references do not teach or suggest every element of the pending claims. In addition, Applicants submit that there would not have been a reasonable expectation of success in combining the references as suggested by the Examiner.

A. LAMBERT IS NOT PRIOR ART AGAINST THE PRESENT APPLICATION

With regard to Lambert, Applicants submit that invention, i.e., conception of the presently claimed subject matter, coupled with due diligence to a subsequent reduction to practice, occurred on a date prior to March 3, 2003, i.e., the earliest possible effective filing date of Lambert. Therefore, it is submitted that Lambert is not prior art against the presently claimed subject matter within the meaning of 35 USC §§ 102 and 103. As evidence of this, Applicants submit herewith a declaration executed by the Chief Executive Officer of Bio-Rad Haifa, Tsafrir Bravman (herein after the Bravman declaration), as well as Annexes A-C.

Applicants submit that the Bravman declaration outlines various facts supporting the assertion that the presently claimed subject matter was invented, i.e., conceived, coupled with due diligence to a subsequent reduction to practice, prior to the effective date of Lambert as a reference against the claimed subject matter.

As indicated at paragraph 7 of the declaration, conception and reduction to practice of the presently claimed *ProteOn* technology was made as early as June 14, 2002. Annex A, submitted herewith as a part of the declaration, is a copy of an electronic document that describes *ProteOn* microfluidics technology. As shown on page 1 of Annex A, i.e., the 'File Properties' page, Annex A was created on June 14, 2002. *See* the Bravman declaration at paragraph 10. Annex B is a document which

summarizes the details of a technological meeting held on September 24, 2002 to discuss the presently claimed subject matter. *See* the declaration at paragraph 14. Annex C is an internal document which was distributed at Bio-Rad Haifa noting the achievements in various aspects of the *ProteOn* project, i.e., the subject of the presently claimed subject matter. Annex C is dated February 2, 2003. *See* the declaration at paragraph 17.

Applicants respectfully submit that the declaration and Annexes A-C demonstrate, that inventors conceived and continually reduced the invention to practice until the actual date of filing of the earliest possible effective filing date of the Lambert publication, i.e., prior to March 3, 2003. At no point along the way did the inventors or the applicant abandon the claimed subject matter. For at least the reason that Lambert is not prior art against the present application, Applicants submit that a *prima facie* case of obviousness has not been established.

B. ALL ELEMENTS ARE NOT TAUGHT OR SUGGESTED BY THE COMBINATION OF REFERENCES

However, assuming *arguendo* that Lambert is prior art against the present application, the presently claimed subject matter is non-obvious because, whether taken alone or together, none of the cited references teach or suggest every element of the presently claimed subject matter.

Claim 29 is directed to a method for determining one or more kinetic parameters of binding between a first binding member and a second binding member comprising: simultaneously adsorbing the first binding member to a surface at a plurality of microspots, the adsorbing comprising activating the surface of at least one microspot by

presenting thereto a chemical activating substance, the activating comprising forming a first channel around a region containing the at least one microspot, introducing a solution containing the activating substance into the channel, and removing excess activating solution from the channel, adsorbing the first binding member to the at least one microspot, and deactivating the at least one microspot; simultaneously presenting the second binding member at a plurality of concentrations to the first binding member at the plurality of microspots, there being a plurality of combinations of first binding member surface density and second binding member concentration among the plurality of microspots; simultaneously obtaining one or more kinetic parameters indicative of a binding reaction between the first and second binding members at each of the plurality of microspots to produce a kinetic analysis of the binding, the binding being detected by a biosensor detection method; simultaneously obtaining reference data from a plurality of interspots, each of the interspots located at a surface between at least two or more the microspots; and processing the binding kinetic parameters and the reference data to obtain one or more kinetic parameters characteristic of the binding between the first and second binding members, wherein the plurality of bindings carried out does not require a regeneration step. Claims 30, 31, 33, 36, 36 and 41-43 depend, either directly or indirectly, from claim 29.

Claim 37 is directed to a method for localizing a molecular species at each of two or more microspots on a surface, comprising: activating a microspot surface by: forming a first channel around the region containing the microspot; introducing a solution containing an activating substance into the channel; and removing excess activating solution from the channel; simultaneously adsorbing a molecular species to each of the two or more

microspots, the adsorbing comprising forming at least two further channels, each being perpendicular to the first channel; simultaneously introducing a solution containing the molecular species into the channel; and optionally deactivating the microspot, wherein the molecular species localized on the two or more microspots may be the same in each of the microspots or different in each of the microspots, and wherein the molecular species may be adsorbed at identical or different surface densities to each of the microspots. Claim 46 depends indirectly from claim 37.

Winkler et al. is directed to method and device for forming large arrays of polymers on a substrate. Ivarsson is directed to a method of examining thin layer structures on a surface for differences in respect of optical thickness. Lambert is directed to methods for normalizing for variations in signal intensity observed in biomolecular binding assays carried out in flow cell cartridges. *See* each of Winkler et al., Ivarsson and Lambert at the respective abstracts.

However, unlike the presently claimed subject matter, Applicants respectfully submit that, whether taken alone or in combination, none of the cited references teach or suggest simultaneously adsorbing as described in claims 29 and 37.

Conventionally, to determine a kinetic parameter of, e.g., association and dissociation rate constants (k_a and k_d, respectively), for the interaction between two interacting molecules (i.e., a first and second binding members in claim 29), one of the molecules is immobilized to a sensor surface and the other molecule, often referred to as the analyte, is provided in solution at several different known concentrations.

The conventional method at the time of filing of the present application was to bring different analyte concentrations into contact with ***the same first binding surface***. Such contact of different sample concentrations with the ***same*** first binding surface provides inherent measurement reproducibility resulting from using the same first binding member. Naturally, such reproducibility is of critical importance in determination of a kinetic parameter, which is a very sensitive procedure in contrast to mere detection of a binding reaction.

Conducting such contacting with ***the same first binding surface*** dictates ***serial*** analysis, an experiment performed along a linear time line each time section is devoted to a particular sample concentration. This view was also made of record in Prof. Gideon Schreiber's affidavit, stating that the paradigm at the time was that kinetic analysis required serial operation and performance of a regeneration step.

Applicants respectfully submit that in the Official Action, it appears that the Examiner mistakenly confuses, and therefore alternates, between discussions of serial processing and parallel processing. However, Applicants submit that at the time of filing of the present application one of ordinary skill in the art would not go against an existing protocol according to which the same first binding member surface would be repeatedly used in an experiment.

For one of ordinary skill to even consider conducting parallel processing of a plurality of analyte concentrations, he/she would first have to decide to move away from the conventional method, which dictates flowing different sample concentrations to contact ***one and the same first binding surface***. Applicants submit that this dictates ***serial*** analysis of the same first binding member and thus requires regeneration.

Turning to Winkler et al., Applicants note that Winkler et al. state that:

> [t]he present invention relates ***to the field of polymer synthesis***. More specifically, in one embodiment the invention provides an improved method and ***system for synthesizing arrays of diverse polymer sequences***. (Emphasis added). *See* Winkler et al. at column 1, lines 7-10.

The inventors of Winkler et al., by their own admission indicate that "...[t]he process is repeated ... By virtue of the process, ***a number of polymers having diverse monomer sequences*** such as peptides or oligonucleotides are formed on the substrate at known locations." (Emphasis added). *See* Winkler et al. at column 2, lines 17-20.

Applicants submit that the binding reactions in Winkler et al. merely assess if one or more of the "diverse peptides" binds a receptor. For example, according to Winkler et al. at column 6, lines 15-20 e.g., "in preferred embodiments the invention provides for screening of peptides ***to determine which if any of a diverse set of peptides has strong binding affinity with a receptor*** and, in most preferred embodiments to determine the relative ***binding affinity of various peptides with a receptor of interest*** such as an antibody." Therefore, Applicants note that, for example, Winkler et al. tests whether any of proteins A, B, ... D bind with a receptor, R. Applicants respectfully submit that this may be referred to as "many proteins to one receptor."

The technology in Winkler et al. merely includes binding reactions to test whether a receptor binds (or relatively binds) any of the ***diverse peptide sequences*** being synthesized.

As discussed herein below, Winkler et al.'s description of delivery of molecules by gravity assisted free-fall and/or pipettor placement, and/or conventional channeling

techniques to pull molecules along the channel blocks, would not lead one of ordinary skill in the art to abort the conventional protocol, which dictates repeated serial reactions on the same binding surface.

Applicants submit that this is completely different from the presently claimed subject matter which recites the determination of ***a kinetic parameter*** (e.g., K_d and K_a) of ***a protein pair*** (i.e., first and second binding members combinations such as those in claim 29) by parallel analysis of different analyte concentrations (e.g., the second binding member in claim 29) at a plurality of microspots.

Applicants submit that none of the references cited directs one of ordinary skill in the art to combine molecules as claimed, i.e., "***a plurality of combinations of first binding member surface density and second binding member concentrations***." Instead, Applicants submit that the cited art suggests repeated experiments on the same first binding member surface.

Applicants respectfully submit that:

(I) whether taken alone or in combination, none of the cited references teach or suggest "simultaneously adsorbing the first binding member to a surface at a plurality of microspots," as recited in the pending claims;

(II) whether taken alone or in combination, none of the cited references teach or suggest a "plurality of combinations of first binding member surface density and second binding member concentrations among the plurality of microspots," as recited in the pending claims; and

(III) the general disclosure of a "simultaneous analysis" does not necessarily describe the determination of a kinetic parameter, e.g., Kd and Ka, or a "plurality of

combinations of first binding member surface density and second binding member concentrations," as claimed.

With regard to item (I) Applicants submit that the process of binding the ***first*** binding member descried by Winkler et al. cannot be considered "simultaneously adsorbing…," as claimed. In this regard, Applicants submit that Winkler et al. describe a ***serial multi-step process to synthesize the first binding member***, i.e., a *de-novo in-situ* gradual coupling of building blocks to create a first binding member on the surface. Applicants note that this process includes building of one monomer (amino acid) on top of the former until the whole polymer (peptide) is gained. Additionally, it includes many chemical steps, washing steps, rotation of channels or opening valves. However, Applicants submit that even if the monomers are transported to more than one spot, there is no disclosure of ***simultaneous adsorbing of the first binding member***.

Moreover, as the technique described by Winkler et al. forms ***a diverse array of peptides***, there is no suggestion of synthesizing the first binding member in more than one spot, let alone "adsorbing" the first binding member in plurality of microspots. Thus, "simultaneously adsorbing the first binding member to a surface at a ***plurality*** of microspots" is not disclosed by Winkler et al. Further, the remaining references do not remedy the deficiencies of Winkler et al. Therefore, the cited references do not render the presently claimed subject matter obvious.

Regarding item (II) above, Applicants submit that Winkler's "many proteins to one receptor" technique, described above, does not teach or suggest the claimed features even if the receptor is provided in different concentrations, e.g., Winkler et al. do not

teach or suggest the combination of a first binding member surface density and second binding member: (A,B_1) and (A, B_2), and (A,B_3), where A is a specific immobilized first binding member and B_x is a second binding member solution of concentration x.

More specifically, the technique described by Winkler et al. forms a diverse array of peptides with maximal number of different (diverse) peptides. Winkler et al. do not teach or suggest providing "a method for determining one or more kinetic parameters of binding between a first binding member and a second binding member .... there being a plurality of combinations of first binding member surface density and second binding member concentrations among the plurality of microspots…to obtain one or more kinetic parameters characteristic of the binding between the first and second binding members, as recited, in claim 29.

With regard to item (III) above, the Examiner states that

> Thus the skilled artisan is suggested to utilize known photodetection techniques, such as that disclosed by Ivarrson that provides the ***benefit of simultaneous analysis, such as kinetic analysis of different sensor zones***. *See* the Official Action at page 8, 3rd paragraph.

In fact, Ivarrson merely describes photo-detection techniques that may occur simultaneously. The Examiner acknowledges that Ivarrson does not describe determination of a kinetic parameter, i.e., "…simultaneous analysis, such as kinetic analysis." Applicants submit that the single phrase in Ivarrson, according to which "mass distribution kinetic data for, e.g. sample binding/desorption" (*see* Ivarrson at column 23, line 63), is too general and unclear to be taken as meaning a "plurality of combinations of first binding member surface density and second binding member concentrations among the plurality of microspots," rather than the conventional

recurrent use of the same first binding member. Thus, Applicants submit that the cited art does not rise to a determination of a kinetic parameter obtained from the combinations, as claimed by the pending claims.

In this regard, Applicants submit that there is no disclosure in any of the references cited by the Examiner that an experiment to determine a kinetic parameter, which by convention is conducted on the same first binding surface, could ever be performed on a plurality of different binding surfaces. Accordingly, Applicants submit that there is no teaching or suggestion, in any of the cited references to abort the inherent reproducibility of serial analysis for parallel analysis with the Winkler et al. device.

Applicants respectfully submit that neither Ivarsson nor Lambert remedy the deficiencies of Winkler et al. Accordingly, every element of the claimed subject matter is not taught or suggested by the combination of references. Therefore, the claimed subject matter is not obvious.

C. NO REASONABLE EXPECTATION OF SUCCESS

The Examiner states that:

> [g]iven the improvements of Ivarrson, the skilled artisan would have had reasonable expectation of success in providing such improvements to the Winkler et al. invention to allow for simultaneous analysis in the different zones. See the Official Action at the bottom page 8.

As previously stated, the presently claimed subject matter is directed to more than simultaneous analysis in the different zones. Applicants submit that neither Winkler et al. nor Ivarrson teach or suggest obtaining a "plurality of combinations of first binding member surface density and second binding member concentrations among the

plurality of microspots," as claimed. Rather, Applicants submit that the cited art merely suggests the conventional recurrent use of the same first binding member. Kinetic parameter determination obtained from the arrived combinations is not taught or suggested by any of the cited references.

Nonetheless, the Examiner appears to propose a device combination to conduct parallel analysis and processing of a plurality of analyte concentrations to produce kinetic analysis instead of the serial techniques in the state of the art.

At the bottom of page 6 of the Official Action, the Examiner indicates that:

> [g]iven that different solutions are provided through different channel, as discussed further above, it is understood that the different concentrations are provided in different channels.... Using the Winkler device as discussed above does not necessitate a regeneration step in order to provide the different concentrations of analyte since they are provided through the different channels and detected simultaneously.

Applicants submit that the Examiner's statement that parallel analyte processing to determine kinetic parameter was readily available is without merit and should be withdrawn. In this regard, the state of the art prior to the filing of the application can be appropriately derived from Rebecca L. Rich, David G. Myszka, *Higher-throughput, label-free, real-time molecular interaction analysis*, Analytical Biochemistry, 361 (2007) 1–6, a 2006 publication cited in a previously filed Information Disclosure Statement.

Applicants submit that the Rich publication reviews the development of kinetic analysis starting from the 90s until about 2006. The only two *parallel analyte processing* systems for determination kinetic parameter are that of Biacore A100 and the ProteOn XPR36, which is owned by the assignee of the present subject matter. Both devices were made available to the public around 2005.

According to the Rich publication at page 4, right column:

> The ***Proteon system [i.e, the technology claimed in the present application] also introduces a novel concept in kinetic analysis*** referred to as "one-shot" kinetics. ***With this approach one can simultaneously test six different concentrations of analyte over the different target surfaces,*** thereby generating a full analyte concentration series with one injection [25,26]. This reduces analysis time significantly and eliminates the need for surface regeneration.

In addition, in a separate 2006 publication, i.e., Bravman T, Bronner V., Lavie K., Notcovich A, A. Papalia G , Myszka DG, *Exploring "one-shot" kinetics and small molecule analysis using the ProteOn XPR36 array biosensor*, Analytical Biochemistry, 358 (2006) 281-288 (herein after the Bravman publication), the following was stated:

> The use of crisscrossing flow paths provides for a number of interesting experimental applications. One of the first applications we wanted to explore was the ability to ***collect kinetic data for six different concentrations of analyte at the same time. Historically, response data for different analyte samples have been collected sequentially. Parallel collection of different analyte concentrations could improve sample throughput and also render obsolete the need to regenerate the target sensor surface***." (Emphasis Added). *See* the Bravman publication at page 282, left column, second paragraph.

This is further supported by US Published Patent Application No. 2005/0014179 (the '179 application), assigned to Biocore and previously cited by the Examiner. Paragraph [0006] of the '179 application recognizes that:

> ***Conventionally, to determine, for example, association and dissociation rate constants (k_a and k_d, respectively) for the interaction between two interacting molecules, one of the molecules, often referred to as the ligand, is immobilized to a sensor surface and the other molecule, often referred to as the analyte, is provided in solution at several different known concentrations.*** Each concentration, or sample, of the analyte is then contacted with the sensor surface, either in a laminar flow past the sensor surface, or in a cuvette or the like, to permit association of the analyte to the sensor surface. After a sample has been brought to contact the sensor surface, the surface is contacted with a solution free from analyte, usually buffer, to permit

> dissociation of the analyte from the immobilized ligand. During these association and dissociation phases, the amount of binding of analyte to the surface is continuously detected and the binding data is collected. ***Before contacting the sensor surface with sample of a new analyte concentration, the ligand surface is restored or "regenerated" by treating the surface with a regeneration solution capable of removing any bound analyte while not destroying the ligand. In that way, all the different samples will contact essentially one and the same ligand surface as far as ligand density is concerned.*** The association and dissociation rate constants can then be obtained from the collected binding data by fitting the data to mathematical descriptions of interaction models in the form of differential equations. Usually, the binding data for all the samples are used in the same fit, a procedure referred to as global fitting. From the determined association and dissociation rate constants k_A and k_d, the equilibrium constant, K_D, and the affinity constant K_A (K_A =1/ K_D) of the interaction can in turn be calculated. (Emphasis Added).
>
> Paragraphs 15 and 16 of the '179 publication goes on to indicate that:
>
> ***[f]rom the prior art it may therefore be concluded*** that for determining kinetic rates for molecular interactions using systems based on biosensors and affinity analysis, ***it is necessary to regenerate the immobilized ligand prior to contacting the sensor surface with a different concentration of analyte to thereby present essentially one and the same ligand surface to each analyte concentration,*** unless (i) a continuous gradient of the analyte is used, or (ii) initial binding rates are determined in systems free from mass transport limitations.
>
> It is an object of the present invention to provide a sensor-based method for determining chemical interaction parameters, including kinetic rate constants, by stepwise titration, which method obviates regeneration procedures while permitting measurements under mass transport limitation. (Emphasis Added).

As already stated, for one of ordinary skilled to even consider conducting parallel processing of plurality of analyte concentrations, she would first have to decide to move away from the conventional method, which dictates flowing different sample concentrations to contact ***one and the same first binding surface***.

Therefore, Applicant respectfully submits that at the filing date there was "no reasonable expectation of success" to conduct parallel analysis and processing of a plurality of analyte concentrations over a plurality of binding surfaces to produce kinetic analysis instead of the serial techniques in the state of the art. On the other hand, there was a reasonable expectation that a regeneration step would be required.

Applicants submit that there is no "reasonable expectation of success" because of the technological limitations in the device of Winkler et al. Figures **4A-4B** of Winkler et al. and the accompanying text reveal that the Winkler et al. device is inappropriate for the use in determining a kinetic parameter, for at least the following reasons: (1) the process of binding the **first** binding member is actually a process of artificial synthesis of a first binding member; (2) the repeated synthesis cycles are likely to insert additional unpredictable variables; (3) The gravity assisted free-fall delivery technique described by Winkler et al. is vulnerable to inaccuracies and is incompatible with determination of kinetic parameters; (4) the lack of uniform surface densities shown in Winkler et al. is incompatible with the aim of determination of a kinetic parameter; (5) the Winkler et al. device is a synthesis platform; and (6) the second binding member in Winkler et al., i.e, the receptor molecule, is merely used for evaluation of relative binding affinity.

With regard to item (1), the process of binding the **first** binding member is actually a process of artificial synthesis of a first binding member. Winkler et al describe a ***serial*** multi-step process that contains building of one monomer (amino acid) on top of the former one until the whole polymer (peptide) is gained. It includes many chemical steps, washing steps, de-protecting steps, rotation of channels or opening valves.

This technological limitation of *de-novo in-situ* synthesis the first binding member (instead of adsorbing the first binding member in claim 29) dictates that Winkler cannot verify that all proteins synthesized are uniformally created (in terms of sequence and/or spatial distribution on the spot).

Moreover, it is further known that amino-monomers coupling inefficiency exists in artificial synthesis of proteins. This inefficiency increases in correlation with the length of the synthesized proteins.

One of ordinary skill in the art would not reasonably expect success by employing the Winkler et al. device, which would bring about any number of unpredictable new variable(s), e.g., coupling inefficiency, distribution of variety of protein sequences, etc., to the determination of a kinetic parameter. As this is already highly sensitive procedure, one of ordinary skills in the art would not resort to a peptide synthesis platform to conduct determination of kinetic parameters.

With regard to (2), the repeated synthesis cycles are likely to insert additional unpredictable variables into the already sensitive procedure of determination of the kinetic parameter.

Regarding (3), figure **4B** in Winkler shows a pipettor **417** which is slidably mounted on arm **419** to deliver selected molecules. In figure **4B**, delivery seems to be actuated in a gravity assisted free-fall manner, from reservoir(s) **421** to flow inlets **411**. The gravity assisted free-fall delivery technique described by Winkler et al. is vulnerable to inaccuracies and is incompatible with determination of kinetic parameters. Similarly, pipettor placement will also result with the same inaccuracies.

With regard to (4), the intensity mapping showed in figures **9**-**10** of Winkler et al. is evidence of increased signal which can be explained by correlation of signal intensity to proximity to the vacuum source to the signal location. Such lack of uniform surface densities, as can be seen in example B and figure **10**, is incompatible with the aim of determination of a kinetic parameter.

Regarding item (5), the channel blocks (**407**) which transport molecules along the substrate defined by Winkler et al. seems to be of much greater dimensions than the microchannels which are utilized by the presently claimed subject matter. Applicants submit that this is inappropriate for the transport of minute solution quantities required for the determination of a kinetic parameter. The Winkler et al. device is a synthesis platform, as previous described, and as such it does not address the required channeling.

With regard to (6), the second binding member in Winkler et al., i.e, the receptor molecule, is merely used for ***evaluation of relative binding affinity***. *See,* e.g., Winkler et al. at column 6 lines, 18-31 and example B. Not only are kinetics not mentioned by Winkler et al., but the proposed array device produces signals which are used for comparative evaluation and not as a mechanism for providing measurements accurate enough for any numerical value.

As stated, the array described by Winkler et al. is designed to screen peptides bind more strongly to a specific antibody by comparing the intensity of a fluorescent signal. Even this works rather roughly due to non-uniform surface densities, as can be seen in example B and figure **10**.

Thus, Applicants submit that the option of using several "receptor" concentrations (col. 11 lines 32-35) cannot be for the purpose of kinetic measurement or for any numerical analysis. In this regard, it is just another option for comparative screening, for which no "reasonable expectation of success" can be attributed to if applied for determination of kinetic parameters.

Regarding the combination of Lambert and Winkler, Applicants submit that one of ordinary skill in the art would not have reasonably expected to solve referencing required for determination of a kinetic parameter by a method addressing other unrelated motivations, e.g., flow rate variation resulting from cartridge structure. In this regard, Applicants note that the Examiner acknowledges that Winkler et al. do not describe "simultaneously obtaining reference data from a plurality of interspots, each of the interspots located at a surface between said at least two or more microspots."

In particular, at according to page 9, lines 19-23

> [t]his is done for normalizing or calibrating for variations in signal intensity due to ***variations in reagent flow rate over the surface of the chip that occur as a result of the contact between the flow stream and the surfaces of the flow cell cartridge***. (Emphasis Added).

In other words, Lambert merely describes calibration of results obtained from binding reaction on a micro chip following ***variations in reagent flow rate over the surface of the chip that occur as a result of the contact between the flow stream and the surfaces of the flow cell cartridge***. In contrast, Winkler solves this problem by use of channel block to transport a molecule. Applicants respectfully submit that this does not involve even scintilla of contact being formed with a cell cartridge. Therefore, one of ordinary skilled would not have had a reasonable expectation of success for

solving the referencing required for determination of a kinetic parameter by a method addressing other unrelated problems.

Finally, Applicants note that at the top of page 8 in the Official Action, the Examiner refers to "surface concentration changes" in Ivarsson at column 23, lines 53-64. However, Applicants note that the subject "surface concentration changes" are actually optical changes being detected \and do not relate to parallel flowing of different analyte concentrations.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, none of the cited references render the presently pending claims obvious within the meaning of 35 USC § 103(a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

IV. At page 11 of the Official Action, claims 32, 44 and 45 are rejected under 35 USC § 103(a) as being unpatentable over Winkler et al., in view of Ivarsson and Lambert as applied to claim 29 above, and further in view of Natesan et al., (US Patent Application Publication No. 20020048792).

The Examiner asserts that "[w]hile Ivarsson discloses only in general kinetic analysis, the skilled artisan would have the knowledge to analyze kinetic parameters such as dissociation constants as such is understood in the art, as shown by Natesan et al."

In view of the following, this rejection is respectfully traversed.

The relevant authority regarding obviousness under 35 USC § 103 is set forth above. For a detailed discussion of the authority on obviousness please *see* § III above.

Claims 32, 44 and 45 depend, either directly or indirectly, from claim 29. The presently claimed subject matter, Winkler et al., Ivarsson and Lambert are discussed in detail above in § III. As discussed: (1) Lambert is not prior art against the present application; (2) the combination of Winkler et al., Ivarsson and Lambert does not teach or suggest every element of the claimed subject matter, and a skilled artisan would not have a reasonable expectation of success in combining the references as suggested by the Examiner.

Natesan et al. is directed to a method for regulated production of a desired protein in cells, which comprises providing cells containing recombinant nucleic acids encoding at least one fusion protein which binds to a selected ligand, wherein the fusion protein comprises a ligand binding domain and a DNA binding domain.

However, Applicants submit that Natesan et al. do not remedy the deficiencies of Winkler et al., Ivarsson and Lambert. Accordingly, the combination of references does not render the presently claimed subject matter obvious.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, none of the cited references render the presently pending claims obvious within the meaning of 35 USC § 103(a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

V. At page 12 of the Official Action, claims 34 and 39 are rejected under 35 USC § 103(a) as being unpatentable over Winkler et al., in view of Ivarsson and Lambert as applied to claim 29 and 37 above, and further in view of Siddigi et al., (US Patent No. 5,541,113).

The Examiner asserts that:

> [w]hile the disclosure [of Siddigi et al.] refers to chemical reaction that can be detected, rather than for immobilizing a probe, the skilledartisan would have recognized that an electric field would induce similar reactions in certain ligands that may be of interest in order to cause a reaction for immobilization purposes, and thus use of an electric field to induce binding in the invention of the combination of the teachings of Winkler et al. and Ivarsson would have been obvious. *See* the Official Action at page 12.

In view of the following, this rejection is respectfully traversed.

The relevant authority regarding obviousness under 35 USC § 103 is set forth above. For a detailed discussion of the authority on obviousness please *see* § III above

Claim 34 depends from claim 29; claim 39 depends from claim 37. The presently claimed subject matter, Winkler et al., Ivarsson and Lambert are discussed in detail above in § III. As discussed: (1) Lambert is not prior art against the present application; (2) the combination of Winkler et al., Ivarsson and Lambert does not teach or suggest every element of the claimed subject matter, and a skilled artisan would not have a reasonable expectation of success in combining the references as suggested by the Examiner.

Siddigi et al. is directed to a method for detecting analyte in an aqueous solution at a physiological pH, by reductive or oxidative electrochemical luminescence methodologies, which method proceeds by labeling the analyte with a transition metal complex, followed by inducing the transition metal label to luminescence by application of a suitable electrical potential to a solution containing the label and the analyte.

However, Siddigi et al. do not remedy the deficiencies of Winkler et al., Ivarsson and Lambert. Accordingly, the combination of references does not render the presently claimed subject matter obvious.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, none of the cited references render the presently pending claims obvious within the meaning of 35 USC § 103(a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

CONCLUSION

In view of the foregoing, Applicants submit that the application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP

/Ari G. Zytcer/
Susanne M. Hopkins
Registration No. 33,247
Ari G. Zytcer
Registration No. 57,474
Customer No. 20529

Date: September 24, 2010
THE NATH LAW GROUP
112 South West Street
Alexandria, VA 22314
Tel: (703) 548-NATH
Fax: (703) 683-8396